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Vancomycin Use Associated with Coagulase-negative *Staphylococcus spp.* Blood Cultures in Children

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Blood cultures serve as the primary way to diagnose bacteremia in children.[1] However, isolation of pathogenic organisms is impacted by several factors, including blood culture volume, number of cultures, collection technique, and timing in relation to starting antibiotics.[2] Unfortunately, blood culture contamination is common in children, with a reported incidence of 0.5% to 22.8%.[3] Bacteria most commonly identified as blood culture contaminants include: coagulase-negative *Staphylococcus* species (CoNS), *Corynebacterium* species, *Bacillus* species (other than anthracis), *Micrococcus* species, and *Cutibacterium* species.[4] Among these, CoNS is the most common, accounting for 70-80% of all contaminated blood cultures.[5]

For pathogenic CoNS, vancomycin is often considered the drug of choice. Exposing children to vancomycin by treating blood culture contaminants of CoNS unnecessarily increases the risk of nephrotoxicity.[4] Studies have identified 28-40% of adults with CoNS contamination are unnecessarily treated with vancomycin (mean duration 5-7 days).[6-8] Additionally, blood culture contamination results in wasted hospital resources, including preparation and administration of unneeded antibiotics, repeat blood cultures, and prolonged length of hospital stay (or admission), increasing the overall cost of care.[1,4]

A knowledge gap exists regarding blood culture contamination and resultant use of antibiotics, primarily vancomycin, in children.[3] The objectives of this study were to evaluate vancomycin use associated with contaminated CoNS cultures in children and identify sub-populations more likely to receive antibiotic treatment. A secondary objective included evaluation of any resulting nephrotoxicity following vancomycin use in these patients. Results from this study will be used to inform future antimicrobial stewardship initiatives related to vancomycin use.

Methods

We performed a retrospective, observational study to evaluate blood culture contamination and resultant vancomycin use as part of a quality improvement initiative. Patients less than 18 years of age with blood cultures meeting our laboratory's definition for contamination and collected from the emergency department (ED) or hospital from January 1, 2015 to December 31, 2018 were included. Repeat episodes of contamination were included for a single patient as long as they occurred in different hospital encounters. The study period began one year post-implementation of the Verigene® gram-positive blood culture nucleic acid test used to rapidly identify select bacteria (including CoNS) and resistance markers from positive blood cultures. Contamination was defined as a single, positive peripheral culture growing CoNS (except *S. lugdunensis*), Streptococcus *viridans* group (except *S.*

TABLE 1. Characteristics of Children with Coagulase-negative *Staphylococcus* Blood Cultures

Characteristics (n=192)	
Age at time of culture (years), median (range)	1.6 (0-17.8)
Female, N (%)	74 (39)
Weight (kg), median (range)	10.5 (0.6-103.5)
Location at time of culture collection, N (%) Emergency department Neonatal intensive care unit Pediatric intensive care unit Ward	 112 (58) 32 (17) 13 (7) 35 (18)
Presence of fever*, N (%)	105 (54.7)
Presence of central line, N (%)	3 (1.6)
Presence of prosthetic device, N (%)	5 (2.6)
Length of stay (days), median (range)	5 (2-33)

**Fever defined as temperature ≥ 38°C +/- 24 hours around culture draw*

anginosus complex), *Cutibacterium* spp., *Corynebacterium* spp., *Micrococcus* spp., or *Bacillus* spp. (except *B. anthracis*). Evaluation of vancomycin use was limited to hospitalized children with CoNS. A subgroup analysis was performed to identify if certain populations were associated with a higher rate of vancomycin use. Patients were excluded if they received vancomycin for greater than 24 hours prior to blood culture or if receiving vancomycin for another serious infection. Patients with renal disease and/or immunodeficiency were also excluded. Nephrotoxicity was defined as doubling of serum creatinine from baseline or absolute rise of 0.5 mg/dL within 7 days of starting vancomycin.

Relationships of categorical patient characteristics with numeric variables were analyzed using Mann-Whitney tests or non-parametric analysis of variance. Non-parametric tests were used due to the skewed distributions of the numeric characteristics. Relationships between various categorical characteristics were analyzed by chi-square tests. Analysis was performed using IBM SPSS Statistics v. 20. This work was deemed exempt by the Children's Wisconsin IRB and designated as a quality improvement project.

Results

Overall, 203 unique cases of a single, peripheral blood culture with growth of CoNS occurred among 190 patients. Eleven children met exclusion criteria, leaving 192 cases from 179 patients for analysis (Table 1). The median age was 1.6 years. Over 50% of children were febrile at the time of blood culture collection. Very few cases had central lines (1.6%) or prosthetic devices (2.6%). Fifty-eight percent of cultures were collected in the ED. For admitted cases, the median length of stay was 5 days.

A total of 186 cases were hospitalized. Of those, vancomycin was prescribed for 88 (47.3%) cases (Table 2). The overall duration of therapy was 3 days (range 1-19 days). There were no differences in vancomycin prescribing rates (data not shown) or duration of therapy (Table 2) by year prescribed or by presence of central line, prosthetic device, or fever. Nephrotoxicity occurred in 5 cases (5.7%).

Overall, 154 (80.4%) cases had a repeat blood culture. Thirty-eight of those had more than one repeat culture. Twelve of the 88 cases who received vancomycin did not have a repeat blood culture. For those 12, the median duration of therapy was 4 days (range 2-8). Of the remaining 76 with at least one repeat culture, the median duration of therapy was 3 days (range 1-19). The difference was not significant.

Therapeutic drug monitoring (TDM) was performed for 69 of the 88 cases who received vancomycin. A plurality of cases (36%) had serum trough concentrations within the 5-10 mcg/mL range (Figure 1). The first serum trough measurement occurred within 2 days for all 69 cases. Twenty-one cases had a level drawn on the same day vancomycin was discontinued.

A total of 83 (45%) hospitalized cases were less than one year of age at the time of blood culture collection (Table 3). Children less than one year of age were not more likely to receive vancomycin than those who were one year of age or greater (p=0.334). However, once initiated, durations of vancomycin were longer in younger patients (6.5 vs. 3 days, p < 0.001).

TABLE 2. Vancomycin Use Among Patients Admitted to the Hospital

Characteristics (n=88)		*P-Value*
Year of therapy, N (% within year of admit) 2015 2016 2017 2018	 17 (45.9) 9 (56.2) 25 (42.4) 37 (50)	0.760
Duration of therapy (days), median (range) Overall Neonatal intensive care unit Pediatric intensive care unit Ward	 3 (1-19) 7 (2-19) 3 (1-10) 2 (1-13)	0.001
Duration of therapy (days) by presence of central line, median (range) Yes No	 5 (1-9) 3 (1-19)	0.876
Duration of therapy (days) by presence of prosthetic device, median (range) Yes No	 5 (3-10) 3 (1-19)	0.305
Duration of therapy (days) by presence of fever* at culture draw, median (range) Yes No	 3 (1-13) 3.5 (1-19)	0.235

**Fever defined as temperature ≥ 38°C +/- 24 hours around culture draw*

Discussion

Unnecessary vancomycin use is a common occurrence when blood cultures are contaminated. Almost half of the cases in our study with a single, peripheral CoNS culture received vancomycin. The overall median duration of therapy was 3 days, which may suggest providers were often using a 72 hour time frame to rule out true bacteremia. Many studies suggest this length of time could be safely shortened to 48 hours or less, particularly in children who arguably had an exquisitely low likelihood of true bacteremia in the first place. We did not identify any differences in vancomycin use over time or by presence of fever, prosthetic device, or central line. This may be due to a lower threshold to initiate treatment in critically ill patients regardless of other clinical factors. Additionally, an apparent "reflex response" to re-admit children with a late positive culture and initiate vancomycin was observed to be a contributing factor. Those children were virtually always afebrile upon readmission. Of the 112 cases in our study who had a contaminated blood culture collected in the emergency department, fourteen were called back to the ED due

TABLE 3. Analysis of Vancomycin Use in Infant Versus Non-infant Children

Characteristics		*P-Value*
Patient age, N (% of hospitalized cases) < 1 year of age ≥ 1 year of age	 83 (44.6) 103 (55.4)	N/A
Received vancomycin, N (% of hospitalized cases) < 1 year of age ≥ 1 year of age	 36 (19.4) 52 (28)	0.334
Vancomycin duration of therapy (days), median (range) < 1 year of age ≥ 1 year of age	 6.5 (2-19) 3 (1-13)	< 0.001

to a positive culture. Ten of those cases were admitted to the hospital, all of whom had negative repeat cultures. Manual chart review identified the reason for admission for all ten cases was related to the positive culture. These admissions were seemingly unnecessary, which has a large impact on patients and families. It could also place the patient at greater risk of contracting a hospital-acquired infection. Additionally this is suboptimal use of hospital resources and may negatively impact healthcare costs.

Unnecessary vancomycin use can result in adverse effects like nephrotoxicity. We found a low rate of nephrotoxicity in our study population (5.7%) compared to rates reported in the literature (as high as 27%).[9-14] We suspect this may be related to the short durations prescribed for a majority of cases.

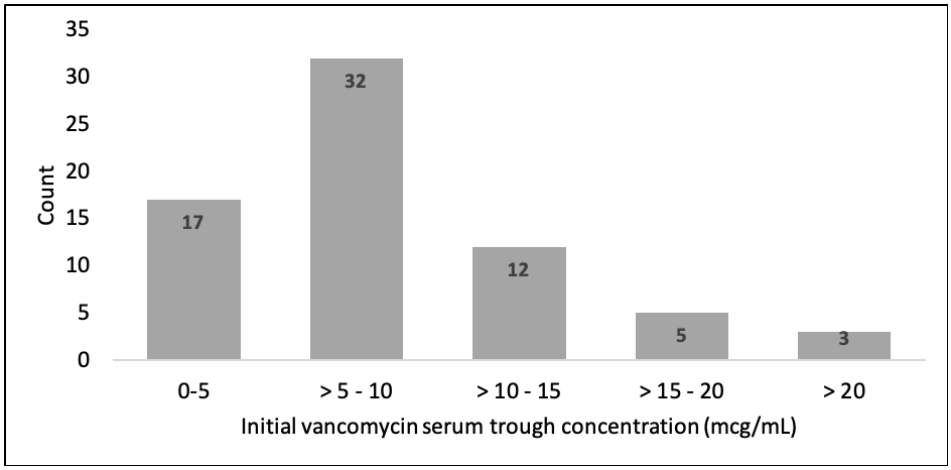
It is important to distinguish between the likelihood of contamination versus true infection to prevent unnecessary utilization of resources. Adult studies have shown that antibiotic stewardship program (ASP) in conjunction with rapid diagnostic testing improves timely organism identification and decreases length of stay and total antibiotic exposure.[15-17]

Contamination is generally presumed for CoNS if only one of at least two blood cultures is positive, especially from a peripheral line and the patient does not have additional risk factors for a true CoNS infection.[18] Reproducibility of subsequent blood cultures is one way to distinguish contamination from true infection. In our study, 80% of cases had at least one repeat culture drawn and almost 20% had more than one repeat. Repeat cultures, especially for patients without a central line and not immunocompromised, appear unnecessary to distinguish contamination from true infection. These excess cultures resulted in increased laboratory workload and potentially prolonged hospitalization. In contrast, 20% of cases never received a repeat culture which, if negative, could have been used to stop vancomycin. It also begs the question why they were ever started on vancomycin if it was felt there was no need to confirm sterilization.

Therapeutic drug monitoring (TDM) is a source of increased costs for patients unnecessarily started on vancomycin. Although new guidelines have been published to guide the use of TDM, these guidelines are limited to *Staphylococcus* aureus infections.[19] In our study, a total of 78% of cases who were initiated on vancomycin received TDM. A third of the cases had an initial vancomycin serum trough concentration in the 5-10 mcg/mL range, which reflects the usual target concentration used at our hospital for sepsis rule-outs. Unfortunately, our data set did not evaluate timing of levels, so we are unable to assess if these represent true steady state concentrations. All cases had vancomycin serum trough concentrations drawn within the first two days of starting vancomycin therapy, before being committed to a full course of therapy. Additionally, a third of cases with TDM had a serum trough concentration drawn on the day of vancomycin discontinuation, resulting in data that could not be used to optimize therapy. The timing and frequency of therapeutic drug monitoring is certainly an opportunity for improvement. Specifically, our antimicrobial stewardship team is advocating for placement of stop dates for antimicrobials, including vancomycin, to indicate the intended duration of therapy (i.e., a 48 hour sepsis rule-out) and lack of need for TDM. As a result, we anticipate a decrease in overall use of TDM, thereby reducing costs and wasted resources, not to mention the distress of an additional needle poke in a child.

We decided to conduct subgroup analyses to identify if certain patient populations were more likely to receive vancomycin. We hypothesized children who were febrile, had foreign bodies present (central lines or prosthetic devices), or were less than one year of age would

FIGURE 1. Initial Vancomycin Serum Trough Concentrations



The bar graph describes initial serum vancomycin trough concentrations for the 69 patients who had therapeutic drug monitoring performed. The x axis represents the initial vancomycin serum trough concentration in mcg/mL. The y axis represents the number of patients who fall within the particular range.

be more likely to receive vancomycin. In spite of these patients being potentially more susceptible to infection, there were no differences in vancomycin prescription rates. However, once started on vancomycin, patients less than one year of age did tend to receive a full rule-out course of therapy compared to those one year of age or greater. We suspect this is due to the contribution of neonatal intensive care unit (NICU) patients in that age group that are generally considered more vulnerable.

Our study has several strengths. First, the study spanned four years of data across all hospital units and the emergency department, thereby decreasing risk of year to year variability. Second, our study period began one year after implementation of a rapid diagnostic test which can provide results within 4 hours (Verigene®), thereby decreasing the time to result notification and decreasing unnecessary use of vancomycin. Finally, we performed manual chart review to assess indication for vancomycin use to identify if there was an alternative indication unrelated to the contaminated blood culture. Our study is not without limitations, however. It was retrospective in nature and occurred at a single center, so results may not be generalizable. The population was not adjusted for known or unknown confounders, which could have limited the results. Furthermore, we had a strict contamination definition, which limited our detection of other organisms and cases which may have represented contaminated cultures. Finally, we limited our population to peripheral cultures only, thus missing patients with contaminated central line cultures.

Conclusion

In conclusion, contaminated cultures pose a significant problem in children. Contaminated blood cultures may result in prolonged hospital stays, increased overall cost of care, and unnecessary antibiotic use (including TDM) which increases risk for complications. Laboratory policies and procedures are needed to limit the evaluation of likely contaminants. Antimicrobial stewardship should implement strategies to reduce unnecessary use of vancomycin and TDM for patients with suspected contaminated cultures.

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